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CASE REPORT

Canine Von Willebrand's Disease: A Common Inherited Bleeding Disorder in Doberman Pinscher Dogs

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Abstract

Von Willebrand's disease is the most common inherited bleeding disorder of dogs occurring with particularly high frequency in Doberman pinscher dogs. Because of its method of transmission (autosomal incomplete dominant), the clinical and laboratory severity of the disease varies considerably. "Stress" may be required to make the increased bleeding tendency clinically apparent. This report describes five cases of Von Willebrand's disease in Doberman pinscher dogs and illustrates the variety of clinical expressions that the disease may take.

Key words: Canine Von Willebrand's disease, case reports.

Résumé

La maladie canine de Von Willebrand, une condition hémorragique héréditaire fréquente, chez le Doberman pinscher

La maladie de Von Willebrand répresente la condition hémorragique héréditaire canine la plus fréquente, surtout chez le Doberman pinscher. Comme elle est attribuable à un autosome de dominance incomplète, la gravité de ses manifestations cliniques et les résultats des épreuves hématologiques présentent des variations considérables. Un stress peut s'avérer nécessaire pour rendre manifeste la tendance accrue au saignement. Cet article décrit cinq cas de la maladie, chez autant de chiens Doberman pinscher, et il en illustre la variété des manifestations cliniques.

Mots clés : maladie canine de Von Willebrand, rapport de cas.

Introduction

Von Willebrand's disease (vWD) is the most common inherited bleeding disorder of dogs. Although first reported in the German shepherd breed, the disorder is now recognized in some 40 breeds of dogs (1,2). It is a particularly prevalent problem in the Doberman pinscher breed. The variability in the expression of canine vWD suggests that, as in man, this disease is likely a spectrum of abnormalities rather than a single defect (3). In Doberman pinscher dogs, the vWD defect is transmitted as an autosomal incomplete dominant trait thus there is considerable variability in the clinical severity of the disease. In this breed, vWD is frequently a relatively mild bleeding disorder requiring some form of "stress" to precipitate a bleeding crisis. The presence of the vWD defect may not be easily recognized by dog owners/breeders or by veterinarians, and mildly affected animals may be utilized in breeding programs and propagate the defect. Veterinarians may recognize the problem only when they undertake surgery on an apparently healthy dog (4). These dogs may bleed profusely resulting in prolonged surgery, increased hospitalization time and increased costs to the owner.

The diagnosis of vWD is based in part on measurements of Factor VIII-related activities. Factor VIII coagulant activity (FVIII:C) may be reduced or within the normal range in the plasma of affected animals. Factor VIII-related antigen (FVIII R:Ag), or von Willebrand factor antigen as it is now known, is usually decreased (5,6,7).

The purpose of this paper is to describe five cases of vWD in Doberman pinscher dogs. These cases illustrate the spectrum of abnormalities that can be seen in this disease and emphasize the often insidious nature of the disorder.

Case #1

The propositus was a seven year old spayed female Doberman pinscher presented for vWD testing because of a history of profuse unexplained bleeding during a previous surgical operation. The dog had been obtained by the present owner when two years of age. The history was uneventful until the dog was six years old. At that time the owner elected to have a small mammary tumor removed and to have the dog spayed. The referring veterinarian reported that excessive and protracted bleeding occurred during surgery necessitating a blood transfusion.

Over the next 12 months the dog developed another mammary tumor. Since the owner wished to have the tumor surgically removed, the referring veterinarian advised presurgical hemostatic testing. Initial screening tests indicated that the platelet count was within normal limits (250 x 10^9/L) and the prothrombin time (PT) and activated partial thromboplastin time (PTT) were also normal. Since these test results did not rule out vWD, the dog was referred for specific Factor VIII assays.

At the time of testing the propositus had not expereinced any other bleeding episodes and had not had any drugs in the previous four weeks. Hemostatic tests at this time revealed a platelet count of 295 x 10^9/L, a normal PT and a slightly prolonged PTT (29% prolongation). Plasma Factor VIII coagulant activity (FVIII:C) was 35% of normal and plasma Factor VIII-related antigen (FVIIIR:Ag) was $< 7\%$ of normal. Normal ranges for FVIII:C and FVIIIR:Ag in our laboratory are 50-150 and 48-161% respectively (4). Examination of the dog's pedigree revealed that the propositus was related to affected dogs on the paternal side, however the status of dogs on the maternal side was not known. Based on the history, pedigree information and laboratory data a diagnosis of canine vWD was made.

Two months later, the mammary tumor was removed. The dog was given 200 mL of fresh normal canine plasma immediately prior to surgery and again during surgery. The surgical procedure was uneventful, however during the next 24 hours bleeding occurred at the incision site and a subcutaneous hematoma developed. An abdominal bandage was applied, however bleeding persisted from the incision site and a subsequent infection of the wound resulted in a prolonged convalescent period.

Case #2

The propositus was a nine week old male Doberman pinscher dog presented for hemostatic evaluation because of problems encountered one week before when it underwent cosmetic otoplasty. This dog was one of a litter of six pups. All littermates had undergone cosmetic tail surgery with no problems reported, however when the ears were cropped, the propositus bled profusely and there was persistent oozing for several days postoperatively. Examination of the dog's pedigree indicated the presence of dogs previously diagnosed to have vWD on both maternal and paternal sides of the pedigree. The parents themselves however, had never been tested. Factor VIII assays indicated a plasma FVIII:C level of 57% of normal and a FVIIIR:Ag level of only 8% of normal in the propositus. A diagnosis of vWD was made.

Both the father and mother were made available for testing. The father was a one year old Doberman pinscher dog who had just sired his first litter and who had no history of bleeding episodes. Plasma FVIII:C activity was 54% of normal and FVIIIR:Ag activity was $< 7\%$ of normal. The mother was a 2.5 year old primipartum bitch who too had no apparent history suggestive of increased bleeding tendency. It was determined however that the bitch had been hospitalized for three days when she had cosmetic otoplasty but the reason for this could not be confirmed. The bitch had a plasma FVIII:C activity of 65% of normal and a plasma FVIIIR:Ag activity of only 11% of normal. Both the dam and the sire were from affected lines. It was concluded that both the dam and sire of the propositus had vWD.

The owner of the bitch elected to have her spayed when her status was identified. The attending veterinarian administered one unit of normal dog plasma before surgery and another unit during surgery. Although it was commented that there was excessive oozing of blood from the initial surgical incision, surgery and recovery were uneventful.

Case #3

The propositus was an 18 month old male Doberman pinscher dog presented for vWD testing because of a history of a severe bleeding episode one month previously. This dog had been obtained at four months of age and no information was available concerning the dog's pedigree. One month prior to presentation the propositus had suffered a severe episode of oral bleeding and the referring veterinarian found substantial ecchymotic and petechial hemorrhages on the oral mucosa. Other mucosal surfaces were unaffected. A coagulogram at that time indicated normal numbers of blood platelets, and a normal activated clotting time, PT and PTT.

Evaluation of FVIII-related activities one month after this crisis revealed plasma FVIII:C and FVIIIR:Ag activities of 61% of normal and $< 7\%$ of normal respectively. A diagnosis of canine vWD was made.

Case #4

A 4.5 year old spayed Doberman pinscher bitch was presented because of the history of a severe bilateral nasal hemorrhage following a traumatic head injury. Two days previously the propositus had been kicked by a horse and suffered a mandibular fracture. Bilateral epistaxis was profuse and persisted for over 24 hours. The referring veterinarian felt that the degree of hemorrhage was not consistent with the severity of the injury and suspected an underlying bleeding disorder, possibly vWD.

The propositus had been obtained at ten months of age by the current owners without pedigree information. At the time of purchase, the dog had already had cosmetic tail surgery and an ovariohysterectomy but had not had cosmetic otoplasty. No information was available concerning the past surgery. According to the owner and referring veterinarian the propositus had been healthy until the present episode.

Factor VIII assays on plasma obtained from the propositus indi-

cated a low normal FVIII:C activity (57% of normal) and a very low FVIII:Ag activity (10% of normal). The laboratory profile was consistent with a diagnosis of canine vWD.

Case #5

A 5.5 month Doberman pinscher bitch was presented for presurgical hemostatic testing because the referring veterinarian felt that the dog might have vWD and the owners wished to have the dog spayed. The present owners had acquired her at six weeks of age as one of only two surviving littermates from a litter of five pups. The cause of death of the other pups had not been determined. One of the surviving littermates reportedly bled profusely when undergoing cosmetic tail surgery but it was not certain whether or not it was the propositus.

When approximately four months of age, the propositus experienced severe oral bleeding of approximately one week duration associated with loss of deciduous teeth. About two weeks later the dog was again examined by the referring veterinarian because of severe diarrhea with some rectal bleeding. Parvovirus infection was suspected. Because of the history and breed of dog, vWD testing was requested prior to ovariohysterectomy.

Plasma FVIII:C activity was 57% normal and FVIIIR:Ag activity was only 9% of normal. The PT was normal while the PTT was prolonged by 84%. The blood platelet count was normal. Examination of the pedigree indicated that the propositus was related on both maternal and paternal sides of her pedigree to dogs known to have vWD. Based on the history, pedigree and laboratory tests, a diagnosis of vWD was made.

The owner elected to go ahead with the ovariohysterectomy. Before surgery could be scheduled however, the propositus came into estrus and the surgery was delayed. The owner reported several days of heavy estral bleeding.

Ovariohysterectomy was scheduled for approximately four weeks after onset of the estral bleeding. During this presurgical period the owner reported that the dog bled for over 20 minutes from a cut foot. Plasma FVIII:C and FVIIIR:Ag activities were redetermined on the day of surgery and were found to be essentially unchanged from the measurements nearly three months before (FVIII:C 55% of normal, FVIIIR:Ag $< 7\%$ of normal). With the informed consent of the owner, the propositus was treated experimentally with the drug desmopression (DDAVP) 60 minutes prior to surgery in an attempt to stimulate increases in plasma FVIII activities and improve hemostasis. Surgery and the immediate postoperative period were uneventful with no excessive bleeding observed and no blood (plasma) therapy was required. The dog was discharged 48 hours later.

Discussion

Canine vWD is often a difficult disorder to recognize because of the variable clinical and laboratory features of the disease, some of which are illustrated by the cases reported here. Genetic abnormalities are frequently recognized early in life and are usually considered less likely in a mature or aged animal. This is not the case in vWD as in this report the initial diagnosis of vWD was made on Doberman pinscher dogs ranging from nine weeks of age to seven years of age.

Because of the way inwhich the vWD defect appears to be transmitted in Doberman pinscher dogs and most other breeds of dogs (autosomal incomplete dominant), both male and female may be affected and the degree of clinical severity can range from severe to relatively mild. As was the situation in three of the cases described, bleeding was only detectable following surgical or traumatic injury.

Spontaneous bleeding from mucous or serosal membranes may result in periodic episodes of melena, epistaxis, hematuria or hemarthrosis. Increased bleeding may be noted when deciduous teeth are shed or during estrus (Case #5). High neonatal mortality and small litters may be associated with vWD. Frequently pups are not necropsied and hemorrhage may not be confirmed as a cause of death. Information concerning cosmetic tail and ear surgery is often inadequate because these elective surgeries may be done before the current owner acquires the animal.

Because of the high incidence of vWD in Doberman pinscher dogs, veterinarians should acquire detailed histories on dogs of this breed presented with hemorrhage or for surgery. Information on related animals, if available, may be useful in ascertaining the relationship of the dog to animals with vWD.

The confirmation of vWD is dependent on specific measurements of Factor VIII-related activities (5,6,7). Hemostatic screening tests such as platelet counts, clot retraction and PT and PTT tests rarely detect vWD since the most consistent finding, with the exception of rare variant forms, is a reduction in FVIIIR:Ag, a protein that plays no role in blood clotting (8,9). Occasionally in vWD the PTT may be prolonged (Case #5). Prolongation of the PTT occurs with low plasma FVIII:C activity (4). Plasma FVIII:C however is frequently within the normal range in Doberman pinscher dogs with vWD. Factor VIII-related antigen levels are frequently so low as to be undetectable ($< 7\%$ of normal), whereas in other Doberman pinscher dogs, the plasma FVIII R:Ag level may be substantially higher. There is some degree of overlap between normal and affected ranges so that affected dogs with FVIII R:Ag levels of 45-55% may not be clearly recognizable. Repeat testing and/or test mating may be required to classify such dogs as unaffected or vWD carriers. Dogs with $> 30\%$ FVIII R:Ag are unlikely to bleed excessively even when stressed (10). Although measurements of FVIII:C are nondiagnostic for vWD, they may have value in predicting the likelihood of bleeding when challenged. The additive effect of impaired blood clotting (as the result of low FVIII:C), superimposed on a substantial deficiency of FVIII R:Ag, predisposes to an increased bleeding tendency. The cuticle bleeding time (CBT) may be a useful presurgical screening test to assess whether the patient is likely to bleed or not; a prolonged CBT however is not necessarily indicative of vWD.

Unfortunately many laboratories do not perform FVIII assays on canine plasmas; techniques used in human laboratories require substantial modi-

fication for use in dogs. The lack of testing facilities has been and continues to be, a major problem in the diagnosis and elimination of canine vWD.

Fresh or fresh frozen plasma (6 mL/kg) should be administered to patients with vWD with a history of prior bleeding who are being prepared for surgery in order to increase FVIII levels. Plasma is preferable to whole blood since more FVIII is given per unit volume, and the need for red cell matching is eliminated. Except in emergency situations, it is inadvisable to administer unmatched blood to dogs with vWD since they are prime candidates for repeat transfusion later in life. Both Case #1 and #2 underwent successful major surgery with prophylactic plasma therapy. Because the half life of FVIII R:Ag is approximately eight hours, more than one transfusion may be required. If hemostasis is not adequate for a long enough period, seroma formation may be excessive and lead to delayed wound healing and/or wound breakdown (as in Case #1).

The vasopressin analog, desmopressin (DDAVP) may have potential value in the treatment and or prevention of bleeding episodes in dogs with vWD (11). This drug induces a rise in plasma FVIII-related activities in normal dogs and studies are currently underway to determine its effectiveness in dogs with vWD. Experimental studies on three Doberman pinscher dogs undergoing major surgery (including Case #5) appeared encouraging. At the present time however, the drug is not approved for this purpose.

References

1. DODDS WJ. Canine Von Willebrand's disease. J Lab Clin Med 1970; 76: 713-721.
2. DODDS WJ. Von Willebrand's disease in dogs. Mod Vet Pract 1984; 65: 681-686.
3. BOWIE EJW. Von Willebrand's disease: State of the art. Scand J Haematol 1984; 33: 431-440.
4. JOHNSTONE IB, CRANE S. Von Willebrand's disease in two families of Doberman pinschers. Can Vet J 1981; 22: 239-243.
5. CHAVIN SI. Factor VIII: Structure and function in blood clotting. Am J Hematol 1984; 16: 297-306.
6. HOYER LW. The factor VIII complex: Structure and function. Blood 1981; 58: 1-13.
7. MARDER VJ, MANNUCCI PM, FIRKIN BG, HOYER LW, MEYER D. Standard nomenclature for Factor VIII and von Willebrand factor: A recommendation by the International Committee on thrombosis and haemostasis. Thromb Haemost 1985; 54: 871-872.
8. JOHNSON GS, TURPENTINE MA, TOMLINSON JL. Detection of von Willebrand's disease in dogs with a rapid qualitative test, based on venom-coagglutinin-induced platelet agglutination. Vet Clin Pathol 1985; 14: 11-18.
9. BENSON RE, JONES DW, DODDS WJ. Efficiency and precision of electroimmunoassay for canine factor VIII-related antigen. Am J Vet Res 1983; 44: 399-403.
10. JOHNSON GS, SCHLINK GT, FALLON RK, MOORE CP. Hemorrhage from the cosmetic otoplasty of Doberman Pinschers with von Willebrand's disease. Am J Vet Res 1985; 46: 1335-1340.
11. JOHNSTONE IB, CRANE S. The effects of desmopressin on hemostatic parameters in the normal dog. Can J Vet Res 1986; 50: 265-271.